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Characterization of the ELSV Transgenic Mouse Model of Pancreatic Carcinoma

Histologic Type of Large and Small Tumors

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Carcinomas of the pancreas that developed in Tg(Ela-1, SV40E)Bri18 and Tg(Ela-1, SV40E+Ela-1, neo)Bri19 strains of transgenic mice were classified into eight histologic patterns. Most were variants of acinar cell carcinoma, but cystic and undifferentiated carcinomas were found. The spectrum of phenotypes was similar in small and large carcinomas, but the small group included a higher fraction of well-differentiated tumors and fewer poorly differentiated and anaplastic tumors. The incidence of islet cell tumors was far higher in the Bri18 strain (77%) than in the Bri19 strain (1.6%). Islet cell hyperplasia was much more prevalent in Bri18 than Bri19 mice. In both strains, the nontumorous pancreas showed acinar cell dysplasia with a more abnormal and distinctive pattern in the Bri19 strain. While the spectrum of exocrine tumor phenotypes is similar, significant differences occurred between these two transgenic mouse strains as models for pancreatic carcinogenesis. (Am J Pathol 1992, 140:1237–1245)

Carcinoma of the exocrine pancreas is a common cause of death from cancer in the US, ranking fourth among men and fifth for both sexes.[1] This reflects the fact that the cancer is usually diagnosed late in its course when it has already achieved an advanced clinical stage that responds poorly to treatment. Animal models have been developed to allow study of causes and development of pancreatic carcinoma. The best characterized models have been established in hamsters and rats.[2] More recently, mouse models for pancreatic carcinogenesis have been developed by introducing viral or human oncogenes under the control of a pancreas-specific promoter into fertilized mouse ova. Virtually all affected progeny of mice bearing *ras* or SV40 early gene constructs developed exocrine pancreatic carcinomas whereas a *myc* construct was nontumorigenic[3,4] in one experiment, and tumorigenic in another.[5] Other transgenic mouse models bearing a transforming growth factor-α construct were nontumorigenic in the pancreas but did induce acinar hyperplasia, formation of tubular ductal complexes, and interstitial fibrosis.[6,7]

The transgenic mice that were used in this project were produced by injection of the promoter/enhancer for the rat elastase-1 gene linked to the genes for SV40 early antigens.[8] The elastase promoter was selected to target the pancreas, and the SV40 early genes to obtain tumor development.[4] ELSV transgenic mice develop hyperplasia and subsequently nodules of the pancreas. Finally, nearly all adult mice bearing this genotype develop carcinomas. Carcinomas develop by 3–4 months of age in three such lines, and by 3–8 months in a fourth line. The tumors often appear to be of acinar cell type.

Goals of our studies of the ELSV model include a more detailed characterization and comparison of this model with other animal models of pancreatic carcinogenesis, and the comparison of the neoplasms that develop in the two strains of ELSV transgenic mice. We have reported separately that there is an unexpectedly high incidence of islet cell tumors in one strain of the ELSV transgenic mice,[9] that there is a clear sex difference in the incidence of exocrine carcinomas (male > female),[10] and that the rate of tumor development can be modulated by diet.[10]

In this article, we describe the spectrum of histologic types of exocrine carcinomas that we have encountered in two strains of ELSV transgenic mice: Tg(Ela-1, SV40E)Bri18, the slow strain, developing tumors in 3–8 months, and Tg(Ela-1, SV40E+Ela-1, neo)Bri19, one of the fast strains, developing tumors by 3–4 months. We compared the phenotype of small tumors with those of large carcinomas as a way of evaluating whether tumor phenotype might be established early and be stable, or

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might evolve with time from well-differentiated to less-differentiated histologic types.

Methods

Transgenic Mice

Founder pairs of strains Tg(Ela-1, SV40E)Bri18 and Tg(Ela-1, SV40E+Ela-1, neo)Bri19 transgenic mice that are homozygous for the elastase promoter-SV40 gene construct were obtained from the laboratory of Dr. Ralph Brinster (Philadelphia, PA). The lines were derived from C57 × SJL hybrids. The mice were housed in a controlled-access animal facility maintained at 21 C with a 12/12 hour light/dark cycle, 2–5 mice per shoebox cage, on aspen shavings. They were given food and water *ad libitum*. Mice were checked daily to monitor health and were weighed weekly.

The mice included in this evaluation were breeding pairs or nonbred mice that were part of dietary studies. The breeders were killed when they were moribund, or showed evidence of abdominal distention. Their ages ranged from 20–36 weeks. The mice that were fed special diets were weaned at the age of 3–4 weeks and fed purified diets until they were 26 weeks of age when they were etherized, killed by guillotine, and underwent autopsy. Some mice became moribund or died before 26 weeks and underwent autopsy at 20–25 weeks of age.

Diets

The breeding colony was fed RMH 3000 chow (Agway, Waverly, NY). At weaning, the pups were placed on one of two diets: AIN-76A purified diet (Teklad, Madison, WI) or a modification of this diet that contained 20% corn oil.

Autopsy

During autopsy, the pancreas was weighed and either fixed completely or sampled for histologic study. Other organs were examined grossly, and abnormal-appearing tissues were sampled for histologic study. Samples of liver, lung, and one gonad were taken for histologic examination when no gross abnormalities were seen. When gross findings were abnormal, additional samples of liver and/or lung were examined. The gonad was included primarily as an internal control for the sex (identity) of the animal but when metastases were identified this was noted. Tissues for light microscopic examination were fixed in Bouin's solution, sectioned, and stained with hematoxylin and eosin or special stains as discussed later. Immunoperoxidase stains using a monoclonal antibody (405) to SV40 T-antigen epitopes[9] were done on selected specimens.

Results

After preliminary histologic evaluation, individual tumors were classified into four primary histologic patterns of exocrine carcinoma and further stratified into eight distinct categories based on architecture and degree of differentiation. The histologic patterns and brief histologic descriptions are listed in Table 1. These patterns are illustrated in Figures 1–8. The classification is based on the apparent dominant phenotype of the epithelial component of the tumor. A few tumors exhibited major components of two distinct patterns, but minor variations of differentiation within a single tumor were deemed insufficient to merit classification as a "mixed" type. Variants of these patterns were noted as follows.

Well- and moderately differentiated acinar cell carcinomas sometimes contained large interstitial spaces filled with protein-rich fluid (Figure 2). In some carcinomas, there were large islands of interstitial fibrous tissue.

Table 1. *Histologic Classification of Exocrine Carcinomas Found in ELSV Transgenic Mice*

Type	Description
Acinar cell carcinoma 1 well differentiated 2 moderately differentiated 3 poorly differentiated	Tumors are composed of acinar cells arranged as acini or tubules with narrow lumens of consistent diameter. The best differentiated tumors were similar to adjacent nontumorous acinar cells. Formation of tubules or acini is rudimentary in the least differentiated tumors.
Undifferentiated carcinoma 4 large cell 5 small cell	Tumors are composed of epithelial cells growing in adherent masses without gland or tubule formation, and without other apparent differentiated features. Large cell variant has a nuclear/cytoplasmic ratio in the range of 0.5 whereas small cell variants have a ratio in the range of 1.
Cystic carcinoma 6 macrocystic 7 microcystic	Glandular tumors with dilated lumenal spaces. The lining epithelial cells may show evidence of acinar cell differentiation, or (rarely) papillary structures. Macrocystic tumors have a fibrous wall whereas there is little stroma within or around the microcystic tumors.
Mixed carcinomas 8 mixed	Two or more of the patterns described earlier are present in a single tumor.

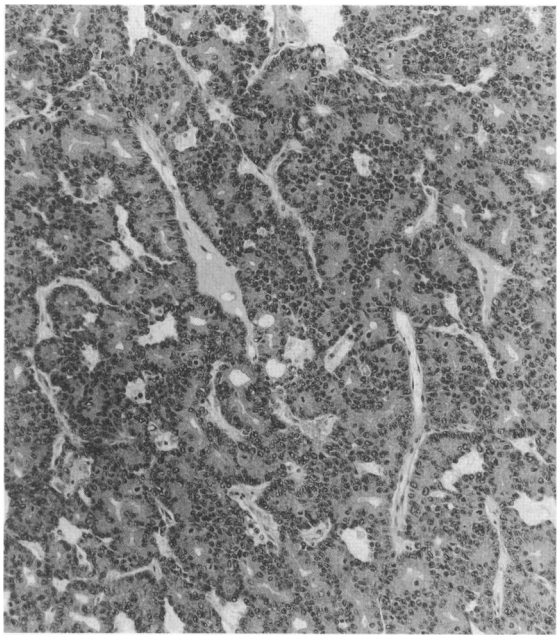

Figure 1. *Acinar cell carcinoma, well differentiated. There is little stroma between the acinar units. H&E, ×88.*

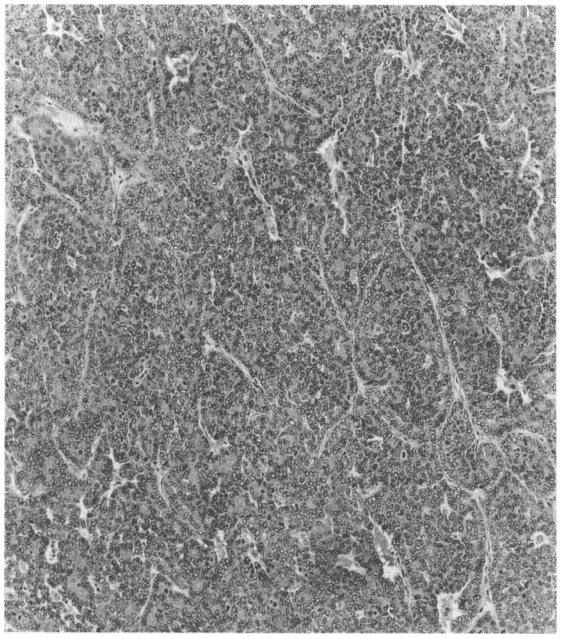

Figure 3. *Acinar cell carcinoma, poorly differentiated. The formation of acinar tubules is discernable, but the cells are small and have few differentiated features. H&E, ×88.*

Evidence was noted of organization of some interstitial transudates, suggesting that this was the mechanism for formation of the interstitial fibrous tissue. Thus, differences in stroma have not been used as a basis for subclassification of the tumors because the major differences in stroma seemed to reflect the epithelial phenotype and age of the tumor.

Cystic tumors appeared to be closely related to moderately differentiated acinar cell tumors since noncystic areas were similar to the latter pattern. The size of the

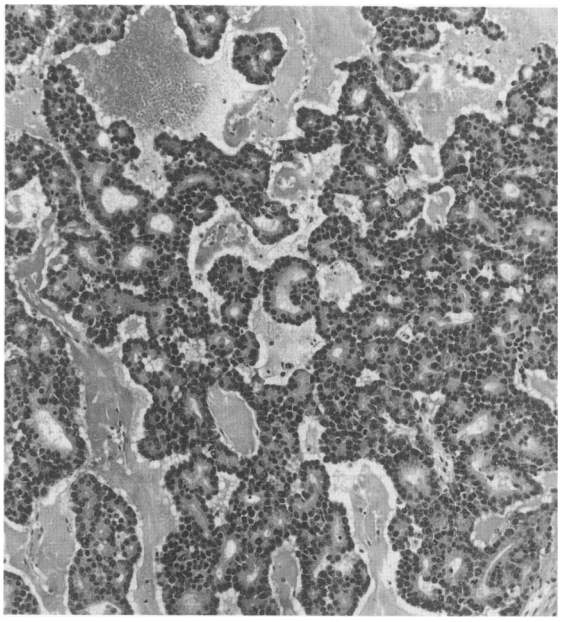

Figure 2. *Acinar cell carcinoma, moderately differentiated. The acinar cells have less cytoplasm than in the better differentiated carcinomas. Some of the tumor cells are separated by protein rich fluid. H&E, ×88.*

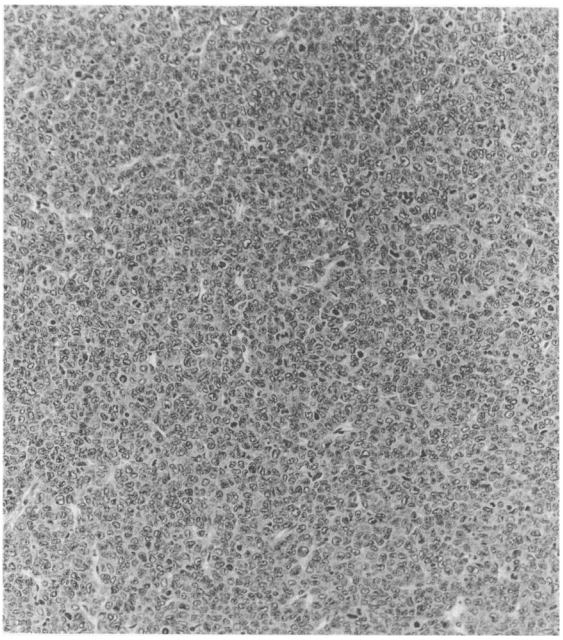

Figure 4. *Undifferentiated pancreatic carcinoma. The neoplastic cells do not form glands or tubules, but still have discernable cytoplasm. H&E, ×88.*

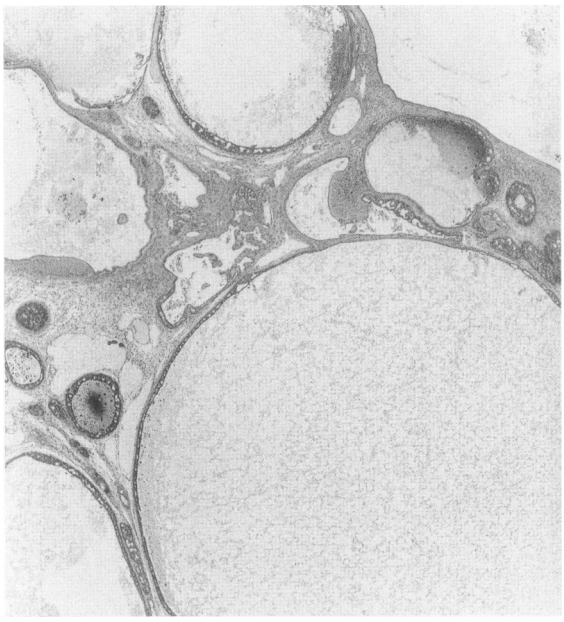

Figure 5. *Cystic pancreatic carcinoma, macrocystic pattern. The neoplastic cells form large cystic spaces surrounded by a dense fibrous wall. Such tumors may be unilocular, or multilocular. H&E, ×16.*

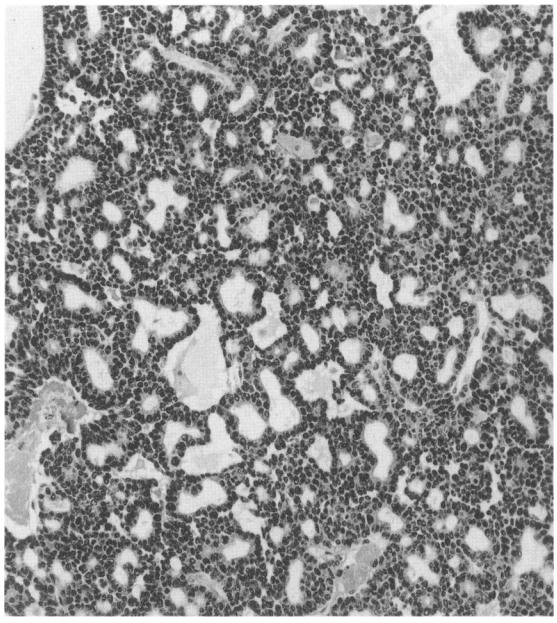

Figure 7. *Cystic pancreatic carcinoma, microcystic pattern. The multiple small cysts are lined by cuboidal or columnar glandular cells that are generally similar to those seen in moderately differentiated acinar cell carcinomas. The lumens often contain homogeneous, eosinophilic material. H&E, ×116.*

cystic spaces was highly variable. Distinct macrocystic and microcystic patterns were present, although microcystic tumors sometimes contained moderate-sized cysts without distinct fibrous walls. A mixed pattern was sometimes seen suggesting that microcystic and macrocystic tumors represent a continuum of cystic tumors. Low columnar cells line cystic spaces in these tumors and occasional cells contained cytoplasmic vacuoles that were mucin positive.

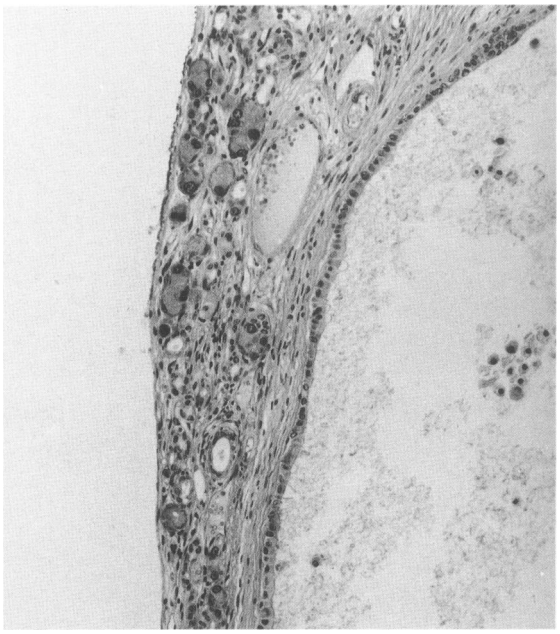

Figure 6. *Cystic pancreatic carcinoma, macrocystic pattern. A low columnar lining epithelium lies on a thick, dense fibrous wall. A few trapped dysplastic acinar cells are present in the wall. H&E, ×116.*

Many of the poorly differentiated acinar carcinomas were composed primarily of sheets of anaplastic cells with focal areas of glandular differentiation. The designation of undifferentiated carcinoma was reserved for tumors in which no glandular differentiation could be identified. The distinction between small-cell and large-cell variants was based on the nuclear/cytoplasmic ratio and most probably represents a phenotypic spectrum.

Some of the undifferentiated exocrine tumors were similar in appearance to some of the more anaplastic islet cell tumors; however, the former did not show endocrine differentiation as evidenced by the absence of islet-cell markers with immunoperoxidase staining.[9] Such tumors showed nuclear staining using a monoclonal antibody to T-antigen (Figure 9). The fraction of nuclei staining and the intensity of the staining were higher in the carcinoma than in the adjacent dysplastic pancreas, which is typical of exocrine tumors (Figures 9, 10). Carcinomas with both exocrine and endocrine differentiation were not identified in these cases.

We compared the histologic type of small tumors, defined as those <3 mm in diameter, and large tumors, defined as those ≥3 mm in diameter. Conventions were adopted as follows: tumors with a maximum diameter of <3 mm in histologic section were arbitrarily classed as

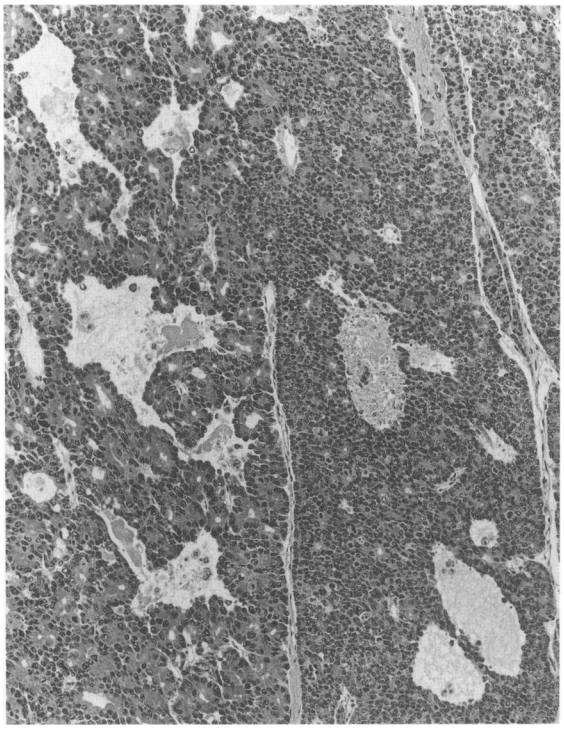

Figure 8. *Pancreatic carcinoma, mixed pattern. The field shows both well differentiated (left) and poorly differentiated (right) acinar cell patterns, apparently within the same carcinoma. H&E, ×88.*

carcinomas *in situ,* and those ≥3 mm were classed as carcinomas even when no metastatic foci were identified. In the absence of strict criteria to identify benign exocrine tumors, the term "adenoma" has not been used. Necrosis was rare in small tumors and common in carcinomas larger than 1 cm in diameter, particularly in the undifferentiated types. Metastases (Figure 11) were seen more commonly when a large primary tumor was present than when primary carcinomas were small.

Four metastatic carcinomas were identified in the Bri18 strain, and seven were identified in the Bri19 strain. The majority of these tumors were moderately or poorly differentiated acinar cell carcinomas. Single examples of microcystic and undifferentiated metastatic carcinomas were also seen. None of the metastatic tumors were well differentiated.

In several pancreases with large tumors, a variable degree of chronic pancreatitis occurred, apparently due to duct obstruction by the carcinoma. In the most advanced areas of chronic pancreatitis, acinar cells were completely atrophic (Figure 12).

Tg(Ela-1, SV40E)Bri18 Strain

The overall incidence of pancreatic exocrine tumors in the mice included in this analysis was 99%. Gross examination of the pancreases revealed tumors ranging from less than 1 mm to 3.5 cm in diameter. Carcinomas in the size range of 3–3.5 cm were common. There were usually multiple tumors per pancreas. The three largest pancreas weights recorded were 7.3, 8.2, and 9.3 g in mice that were 26, 22, and 26 weeks old. The distribution of histologic types for small and large tumors is shown in Table 2.

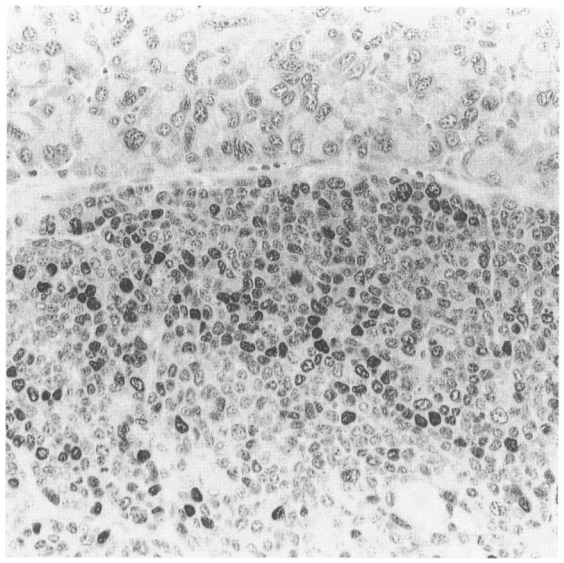

Figure 9. *Exocrine carcinoma stained by the immunoperoxidase method using an antibody (405) to a T-antigen epitope. A variable degree of staining is evident in the nuclei of the tumor cells. The tumor cells (bottom) are more heavily stained than the surrounding pancreas (top), ×175.*

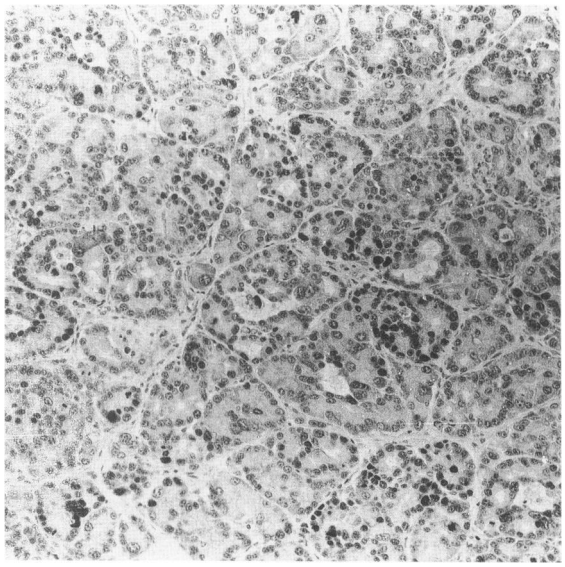

Figure 10. *Dysplastic pancreas stained by the immunoperoxidase method using an antibody (405) to a T-antigen epitope. A variable degree of staining is evident in the nuclei of scattered cells, ×88.*

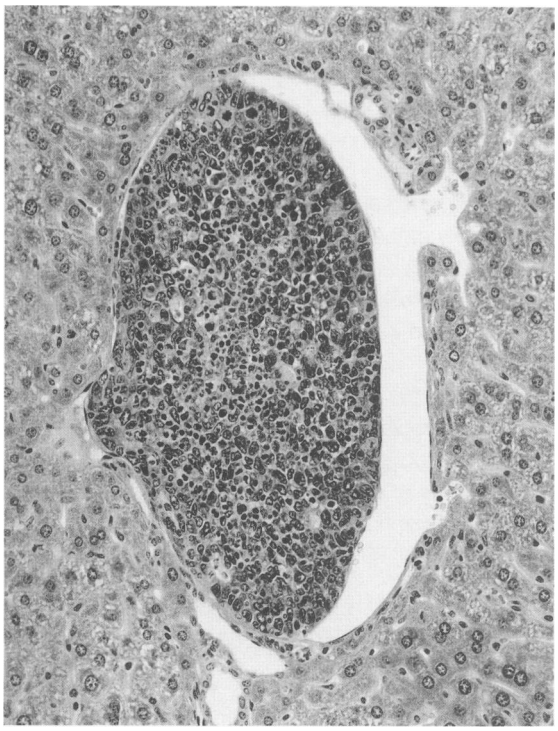

Figure 11. *Hepatic metastasis from an acinar cell carcinoma. Tumor cells occupy a small hepatic vein. H&E, ×175.*

The incidence of islet cell tumors among the Bri18 mice included in this analysis was 77%. The majority of the islet cell tumors were apparently benign or low-grade malignancies (Figure 13), but three were identified as carcinomas on the basis of hepatic metastasis. The largest islet-cell tumors were in the range of 1 cm in diameter. The islet-cell tumors and islet hyperplasia have been described in greater detail separately.[9] The majority of the islet-cell tumors appeared to be composed of β cells with immunoreactivity for insulin, but one tumor had predominant somatostatin immunoreactivity.

Exocrine and endocrine tumors were not distinguished reliably on the basis of gross examination; however, islet-cell tumors were never cystic and usually showed a vascular "blush." Exocrine tumors were often cystic or highly vascular (dark red) and could sometimes be recognized on this basis.

Both small-cell undifferentiated patterns and macrocystic patterns were more frequently encountered in Bri18 than Bri19 strain mice.

The pancreases of all mice included in this study displayed diffuse dysplasia of acinar cells as well as focal changes that appeared to be of a clonal nature inasmuch as the cells within foci or tumors showed less pleomorphism than those of the pancreas in general. Many of the pancreases also showed a characteristic form of islet-cell hyperplasia in which normal-appearing islet cells were surrounded at the periphery by small islet cells (Figure 14).

Tg(Ela-1, SV40E + Ela-1, neo)Bri19 Strain

The overall incidence of pancreatic exocrine carcinomas in the Bri19 mice included in this analysis was 100%. Gross examination of the pancreases showed tumors ranging from less than 1 mm to 8.0 cm in diameter. There were usually multiple tumors per pancreas. The three largest pancreas weights recorded were 9.6, 10.6, and 10.7 g in mice that were 29, 24, and 18 weeks old. The distribution of histologic types for small and large tumors is shown in Table 3.

A single islet-cell tumor was identified in the Bri19 mice included in this analysis, an incidence of 1.6%. This tumor was large (1.2 cm), but no metastases were identified. Immunohistochemical studies confirmed the islet-cell origin of this tumor with insulin immunoreactivity.

Islet hyperplasia of the type reported in Bri-18 strain mice[9] is infrequent in Bri-19 strain mice. The true incidence is difficult to determine because the high incidence of large exocrine tumors interferes with examination of the non-neoplastic portions of the pancreases, but it is estimated to be less than 10%.

A pattern of dysplasia, distinctly different from that identified in the Bri18 mice, was seen in all of the pancreases of the Bri19 mice. The non-neoplastic portions of the pancreases had thin bands of fibrous tissue separating groups of acini into vague lobules. Also, acinar tissue often formed small ringlike structures with central interstitial transudates (Figure 15).

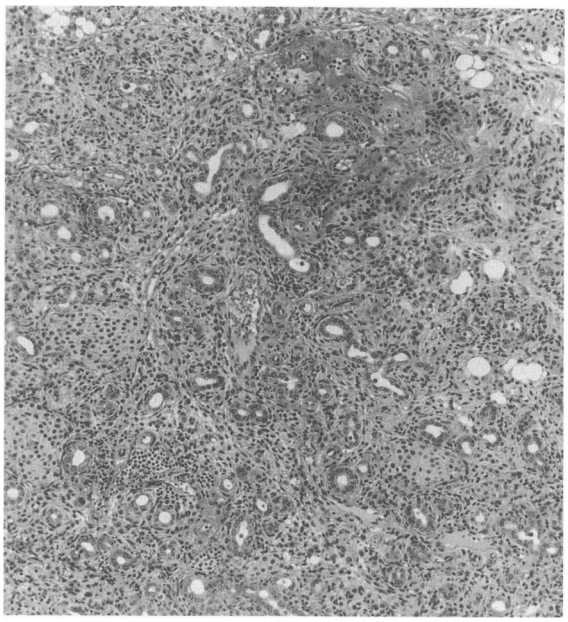

Figure 12. *Chronic pancreatitis with virtually complete atrophy of acinar cells, H&E, ×88.*

Table 2. *Histologic Classification of Tumors in Tg(Ela-1, SV40E)Bri18 Transgenic Mice*

Histologic type		Incidence*			
		Large carcinomas		Small carcinomas	
		(n)	(%)	(n)	(%)
Acinar cell carcinoma	1 Well differentiated	9	10.6	13	15.1
	2 Moderately differentiated	30	35	49	57
	3 Poorly differentiated	27	32	18	20.9
Undifferentiated carcinoma	4 Large cell	4	4.7	2	2.3
	5 Small cell	2	2.4	1	1.2
Cystic carcinoma	6 Macrocystic	3	3.5	0	0
	7 Microcystic	8	9.4	3	3.5
Mixed pattern	8 Mixed	2	2.4	0	0
Total		85	100	86	100

* Incidence as number observed (n) and per cent of the total group of tumors.

Discussion

Nearly 100% of both strains of the ELSV transgenic mice studied developed pancreatic carcinomas. The histologic appearance of the exocrine tumors supports the view that all are of acinar cell origin, as would be predicted from the nature of the transgene. Neither hyperplastic nor preneoplastic ductal abnormalities were identified in the pancreases of ELSV mice. There was no intraductal epithelial hyperplasia or tubular ductal complexes as have been described in carcinogen-treated hamsters.

In both strains, a similar spectrum of tumor types is found in large and small tumors. In general, small tumors tend to be better differentiated than large carcinomas. This suggests that there is a progression of phenotype from well-differentiated to poorly differentiated with growth in some tumors. Alternatively, the fact that a higher fraction of large carcinomas are less differentiated may reflect an accelerated growth rate of poorly differentiated and anaplastic tumors. The finding of individual carcinomas with mixed histologic patterns supports the idea that phenotypic progression toward anaplasia can occur with tumor growth. However, the possibility that such mixed phenotype tumors arose separately as two tumors in apposition cannot be excluded.

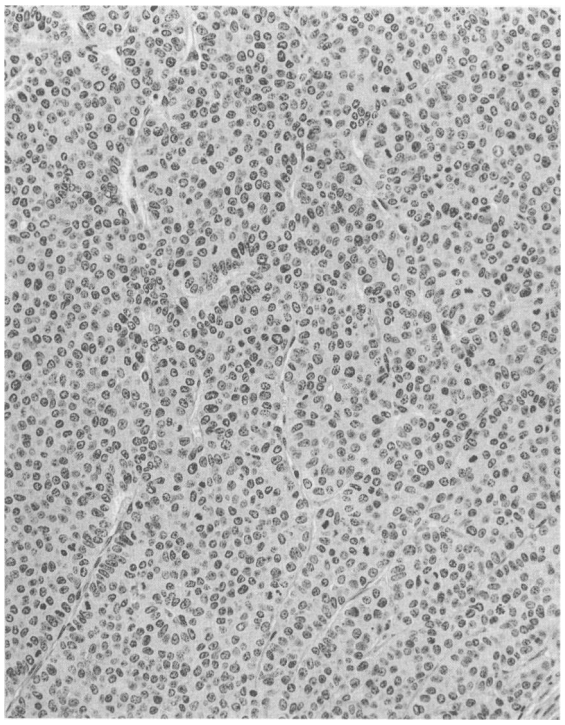

Figure 13. *Islet cell tumor. H&E, ×175.*

Several examples of poorly differentiated small tumors and well- differentiated large carcinomas were also identified in both strains. Thus, at least in some instances, it appears likely that the tumor phenotype is established early and maintained as the tumor grows to large size.

Both strains had diffuse acinar cell dysplasia in the non-neoplastic portions of the pancreas. However, the patterns of dysplasia differed between the two strains. The thin bands of fibrous tissue separating the acini into vague lobules and the small ringlike structures with central interstitial transudates were observed only in the Bri19 mice, suggesting that some uncharacterized factor(s) may affect the interstitial tissues of the pancreas, causing a proliferative response.

The full spectrum of tumor types was recognized in mice fed a chow diet. The same spectrum has been encountered among mice fed the AIN76A diet and a variation of this purified diet without apparent effect of diet on the incidence of the various tumor types. We have previously reported that exocrine tumors develop earlier among Bri18 strain mice fed purified diets compared with chow-fed groups, but the incidence of islet cell tumors was not influenced by these diets.[10] Thus, diet can affect the ratio of exocrine to endocrine tumors in the Bri18 strain. In the same study, we found metastasis of exocrine carcinomas in 3/108 mice (2.8%). All mice with metastasis had been fed purified diets, so it appears possi-

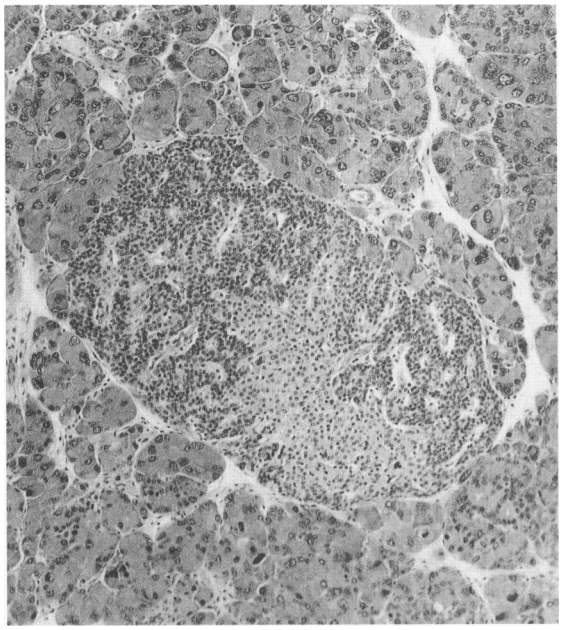

Figure 14. *Acinar cell dysplasia (top and bottom) and islet hyperplasia (center) in a Bri18 mouse. The pale staining islet cells are surrounded by small, darker staining cells with an eccentric distribution. H&E, ×88.*

ble that diet can influence tumor progression. In the Bri19 strain metastases were identified in 5/61 mice (8.2%).

The high incidence of islet cell tumors and islet cell hyperplasia in the Bri18 mice represents an unexpected feature of the model that is not predicted from the transgene.[9] Their presence requires caution and histologic monitoring when tumors are used as a source of nucleic acids or proteins for molecular analysis of the model, or when the incidence of tumors determined grossly is used as a parameter of exocrine pancreatic carcinogenesis.

The induction of exocrine pancreatic carcinomas in rats by azaserine (O-diazoacetyl-L-serine) has provided an extensively studied model of pancreatic carcinogenesis.[12] Foci, nodules, and adenomas of atypical-appearing acinar cells that maintain a high degree of differentiation are induced by azaserine. This suggests that acinar cells are the principal or only target of azaserine in the rat pancreas in regard to the production of proliferative lesions with neoplastic potential. The acinar cells in such lesions maintain a diploid nuclear DNA content,[13] and show less cellular dysplasia than is seen diffusely in the pancreases of ELSV mice. The carcinomas that develop in azaserine-treated rats include a broad spectrum of histologic variants. A series of such carcinomas has been classified[14] and includes tumors that are similar to the histologic types seen in ELSV mice. The microcystic pattern is much more frequent in the mouse model than in the rat model. Rat carcinomas more frequently contain ductlike areas. The stromal changes of vascular lakes and interstitial fibrosis are more frequent in the mouse model.

Carcinomas in rats are diagnosed on the basis of histologic evidence of anaplastic cellular changes, evidence of invasion, or metastasis. Localized carcinomas (carcinoma *in situ)* have been identified as early as 4 months after initial treatment with azaserine, but are more frequently found in experiments of more than 6 months in duration. The ELSV model achieves a much higher incidence of carcinomas in 6 months than was seen in the rat model.

The carcinomas that develop in ELSV mice bear little resemblance to the bulk of carcinomas that are seen in nitrosamine-treated hamsters. The majority of hamster pancreatic carcinomas appear ductlike, although a few are unclassified (anaplastic).[15] Many hamster carcinomas exhibit mucin secretion that was rarely seen in the mouse tumors. The latent period for tumor development in hamsters also exceeds that of the ELSV mice except in recently described, complex regimens that use a combination of high doses of N-nitrosobis(2-oxopropyl)-amine, ethionine injections, and dietary manipulation.[16]

The pancreatic carcinomas that develop in the ELSV transgenic mice are more similar to those in chemically

Table 3. *Histologic Classification of Tumors in Tg(Ela-1, SV40E + Ela-1, neo)Bri19 Transgenic Mice*

Histologic type		Incidence*			
		Large carcinomas		Small carcinomas	
		(n)	(%)	(n)	(%)
Acinar cell carcinoma	1 Well differentiated	12	10	31	27
	2 Moderately differentiated	33	27	47	41
	3 Poorly differentiated	26	21	12	10.4
Undifferentiated carcinoma	4 Large cell	2	2	0	0
	5 Small cell	0	0	0	0
Cystic carcinoma	6 Macrocystic	1	1	3	2.6
	7 Microcystic	39	31	20	17
Mixed pattern	8 Mixed	11	9	2	2
Total		124	100	115	100

* Incidence as number observed (n) and per cent of the total group of tumors.

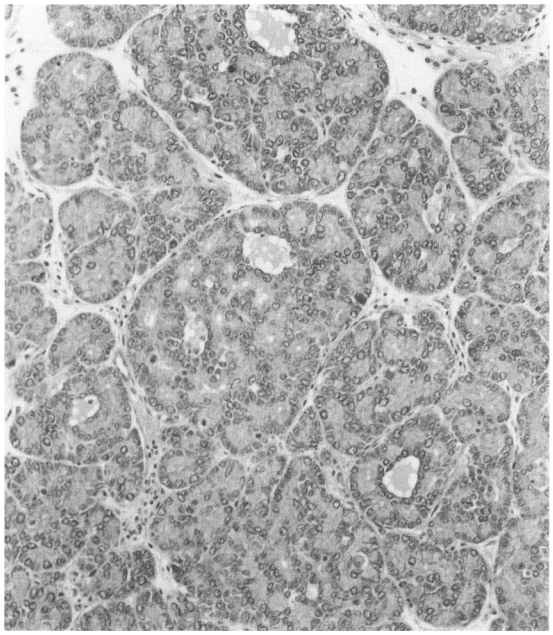

Figure 15. *Acinar cell dysplasia in a Bri19 mouse. Thin bands of fibrous tissue separate groups of acini into vague lobules. Acini often form small "ringlike" structures with central interstitial transudates. H&E, ×88.*

induced models in rats than in hamsters. The appearance of the exocrine tumors suggests that the majority arise from acinar cells as would be predicted from the nature of the transgene. Advantages of this model of pancreatic carcinogenesis are the shorter latent period compared with chemically induced models and the freedom from the need for chemical carcinogens. The acinar cell origin of the carcinomas may be a disadvantage in regard to relevance of this model to the development of human pancreatic cancers.

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